# DEPRESSION IN NEUROLOGICAL DISORDERS: PARKINSON'S DISEASE, MULTIPLE SCLEROSIS, AND STROKE

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Depression is a heterogeneous group of conditions and a clinical diagnosis without external validators. Diagnosis of depression in the setting of disorders that produce psychomotor retardation and changes in vegetative function can be particularly challenging. This review aims to emphasise the importance of depressive symptoms and syndromes in the overall wellbeing of people with neurological disorders, and to equip clinicians with the practical skills to recognise and treat depression effectively.

The evidence base for the treatment of depression in neurological disorders is inadequate. Therefore much of the advice on treatment is based on clinical consensus and experience with treatments in other settings (that is, in the treatment of idiopathic depressive syndromes). Controlled trials of treatments for depression in this setting are urgently needed.

## DEPRESSION IN PARKINSON'S DISEASE

Diagnosis and management of depression in Parkinson's disease (PD) is important for two main reasons: firstly, depression is common in PD (see details on prevalence below), and secondly depression causes significant morbidity in terms of quality of life, disability (measured by activities of daily living), and carer stress. This effect is independent from the effect of motor disability.

### Epidemiology

Estimates of the prevalence of depression in Parkinson's disease vary considerably, mostly because of differences in sampling methods and case ascertainment. Studies based on community samples appear to produce lower prevalence figures. Looking at the studies as a whole, the prevalence of depression in PD is probably between 20–45%, with the lower figures relating to community based studies. There does not appear to be a higher prevalence with either sex.

The relation between depression and the temporal course of the motor symptoms of PD has been studied in different ways. Two well conducted studies have addressed the idea that psychiatric symptoms (particularly depression and anxiety) may precede motor symptoms of PD by a number of years (as often they do in Huntington's disease). These studies used a case–control methodology and found that the odds ratio for a previous history of depression in the PD cases was around 2 compared to controls. The average time between onset of depressive symptoms and motor symptoms was around six years, which correlates well with positron emission tomography (PET) studies suggesting that the onset of the disease process may predate motor symptoms by the same time period.

Some authors have suggested that the prevalence of depression relative to the course of PD is biphasic, with a peak early in the illness (possibly related to increased life events) and another gradual increase as the illness reaches its latter stages (fig 1). Depressive illness also appears to be more common in those people with more rapidly progressive PD. There is no evidence so far that depression is more common in a specific genotype of Parkinson's disease or in one of the "Parkinson's plus" syndromes.

### Diagnosis of depression in Parkinson's disease

Diagnosing depression in PD can be particularly difficult because of the clinical overlap between the two syndromes.

Symptoms that are common to both depression and idiopathic Parkinson's disease include motor slowing, bradyphrenia, sleep and appetite disturbance, weight loss, loss of interest and concentration, and reduced libido. The "body language" of depression looks similar to that of PD at first glance. The patient often appears hunched with a lack of an obvious affective response and spontaneity (the patient with PD may well have an intact affective response but may not be able effectively to translate this into motor phenomena).

Symptoms that may help in the diagnosis of depression in people with PD include;

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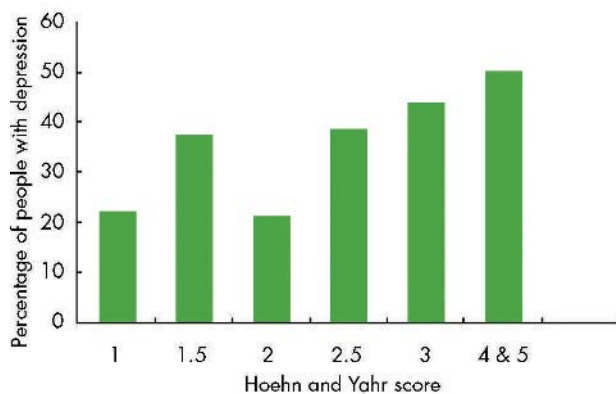
**Figure 1** Depression in Parkinson's disease by Hoehn and Yahr score. Based on data from Schrag *et al. Psychol Med* 2004;**31**:65–73.

- pervasive low mood with diurnal variation (for at least two weeks)
- early morning wakening
- pessimistic thoughts about the world, themselves, and the future (out of context with their level of disability or their previous attribution style)
- suicidal ideation.

Table 1 lists the *Diagnostic and statistical manual*, 4th revision (DSM-IV) criteria for major depressive episode.

Depression should be considered in any patient whose function deteriorates notably over a few days or weeks.

Low mood can also be present as part of other psychiatric disorders. Non-motor fluctuations have been increasingly described in PD. These can usually be discriminated from depression by good history taking. Adjustment disorders are brief changes in mood and function following a significant life event (such as a diagnosis of Parkinson's disease). They may often resolve without active treatment. Depressive symptoms and reduction in function can sometimes represent a prodrome for dementia. Low mood can also occur as a consequence of medications used to treat Parkinson's disease or other conditions (such as hypertension). Other general medical conditions, co-existing with Parkinson's disease, can present with a depressive syndrome (such as systemic infections or subdural haematoma) (table 2).

A variety of mood disorders have been described in the setting of neurosurgery for PD. These include transient

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**Table 1**  DSM-IV criteria for major depressive episode

A Five (or more) of the following symptoms have been present during the same two week period and represent a change from previous functioning. At least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure
1 Depressed mood most of the day, nearly every day, as indicated by either subjective report or observation made by others
2 Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day
3 Significant weight loss when not dieting or weight gain, or decrease or increase in appetite, nearly every day
4 Early insomnia or hypersomnia, nearly every day
5 Psychomotor agitation, nearly every day
6 Feelings of worthlessness or excessive or inappropriate guilt, nearly every day
7 Diminished ability to think or concentrate, or indecisiveness, nearly every day
8 Recurrent thought of death, recurrent suicidal ideation without a specific plan, or a suicide attempt or specific plan for committing suicide

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**Table 2**  Differential diagnosis of depression in Parkinson's disease

- Major depressive episode
- Adjustment disorder
- Mood disorder caused by a general medical condition (infection, subdural haematoma)
- Drug induced mood disorder
- Dementia
- ''Non-motor fluctuation''
- Transient mood changes in relation to DBS (dysphoria, pseudobulbar crying)

DBS, deep brain stimulation.

i49

dysphoria during surgery (especially in relation to stimulation around the subthalamic nucleus). More chronic changes in mood have also been described following pallidotomy and deep brain stimulation although definitive studies have not been performed in this area.

### Scales used to measure depression in Parkinson's disease

As mentioned above, symptoms of idiopathic PD have considerable overlap with those of depression. This means that standard rating scales for depression may not be valid in this situation. Rating scales for depression may be loaded with ''somatic'' or ''vegetative'' symptoms, which reduce their validity.

Three rating scales have been tested using a clinical interview with operationalised diagnosis as a gold standard. Using receiver operating curves, the sensitivity and specificity at a given ''cut off'' point can be calculated. From this methodology, it is clear that the Beck depression inventory is not a useful rating scale in PD. The Montgomery and Asberg depression rating scale (MADRS) and the Hamilton depression scale (HAM-D) have performed better. In summary, diagnosis of depression should be made clinically, using appropriate diagnostic criteria, with severity or response to treatment being measured using MADRS or HAM-D.

### Treatment of depression in the setting of Parkinson's disease

The evidence base for the treatment of depression in PD is extremely slim. A recent Cochrane library review of treatments for depression in PD reported three randomised controlled trials (RCTs) fulfilling the criteria for inclusion.[1] These trials included a total of 106 patients and indicated that nortryptilline was superior to placebo but that citalopram was not. The review concluded that there were ''insufficient data on the effectiveness and safety of any antidepressant therapy in Parkinson's disease''. There is an urgent need for larger scale clinical trials in this area.

Nevertheless, depression is common in PD and decisions have to be made about treatment. The last 10 years have seen a shift in prescribing practice away from tricyclic antidepressants (TCAs) and towards selective serotonin reuptake inhibitors (SSRIs) as a first line treatment of depression in PD. The main reason for this is the more favourable side effect profile of SSRIs.

### Tricyclic antidepressants

The TCAs include amitryptiline, nortryptiline, and dothiepin. Clinical trials in idiopathic depressive illness have shown that these drugs are effective. They have a variety of side effects

including constipation, dry mouth, blurred vision, and sedation which may be particularly troublesome in an elderly population. In higher doses, they are cardiotoxic and can be fatal in overdose. Anticholinergic effects are very common which could potentially help motor disorder but worsen confusion and cause the other problematic side effects listed above.

## Selective serotonin reuptake inhibitors

The SSRIs include fluoxetine, paroxetine, sertraline, fluvoxamine, and citalopram (as well as its isomer escitalopram). Trials in idiopathic depressive disorders have shown them to be effective as a group. Adverse effects can vary between the individual drugs. Common adverse effects include nausea, upper gastrointestinal (GI) disturbance, and changes in sexual function (delay in orgasm and ejaculation, erectile problems). More recently it has been shown that the addition of an SSRI to the treatment regimen of someone already taking aspirin can significantly increase the risk of upper GI bleeding, especially in the elderly. The adverse effects tend to occur early in treatment and also tend to be dose dependant.

Withdrawal syndromes can occur in people who stop SSRIs suddenly and can include flu-like symptoms, insomnia, nausea, imbalance, sensory disturbance, and hyperarousal (FINISH) (table 3). Therefore SSRIs should be reduced slowly.

## Other treatments for depression

Electroconvulsive therapy (ECT) has been used in the treatment of depression in PD and appears to be a safe treatment. However, there are no randomised trials of its use in this setting. Small case series indicate that motor symptoms of PD may be temporarily alleviated by a course of ECT treatment, but that does not change the overall prognosis of the illness. Other antidepressants have been reported in the treatment of PD depression (such as mirtazepine, venlafaxine, and reboxetine) but their role is not clear.

Cognitive therapies have also been used in the treatment of depression in the setting of PD. They have a potential role, especially if the patient may not tolerate physical treatment or is on a complex treatment regimen already. There are also small case series of transcranial magnetic stimulation (TMS) being used to treat PD depression.

## DEPRESSION IN MULTIPLE SCLEROSIS

Depression in its different manifestations is the most common mental disorder in multiple sclerosis (MS). Depressed mood also contributes significantly to reductions in quality of life for people with MS. Therefore it is important to recognise and treat depression appropriately in the setting of MS. On the other hand, the only study looking at health related costs in MS did not indicate that depression led to greater health costs in MS.

### Epidemiology of depression in MS

Many of the earlier studies into prevalence of depression in MS were subject to considerable ascertainment bias. Two recent, community based studies have addressed this problem to some extent. In the first study,[2] subjects from a large community sample were evaluated using the Center for Epidemiological Studies–depression scale (CES-D), which is used to screen for depression in primary care. Forty one per cent of respondents had depression (CES-D score > 16) with a subgroup of 30% having moderate or severe depression (CES-D score > 21). Depression was related to shorter duration of illness. Patten *et al*[3] obtained data from the Canadian community health survey, which looked at health in 115 071 people. The prevalence of depression in MS in this study was 25%. Rates of depression are higher in nursing home settings and one study noted that younger people with MS were more likely to be depressed than their older counterparts with similar levels of physical disability.

### Symptoms of depression in MS

Like Parkinson's disease, vegetative or somatic symptoms do not tend to be good diagnostic discriminators for depression in MS. Some vegetative symptoms may be specifically related to fatigue rather than depression, but this area is fraught with methodological and conceptual difficulties. One study has indicated that ''disinterest in sex'' was uniquely related to depression in MS (rather than fatigue or physical disability). Important clues to depression in MS are illustrated in table 4.

### Suicidal behaviour in MS

Suicidal ideation is very common in MS. In one study, a quarter of clinic attenders with MS had suicidal ideation sometime in the week before their attendance. Around 3% of people with MS will kill themselves. A study of the cause of death in 3000 people with MS over 16 years indicated that 15% of the deaths were recorded as suicide.[4] Other studies have confirmed this increased risk and indicated that additional risk factors for suicide in MS include being male, young age of onset, previous history of depression, social isolation, and substance abuse. A study comparing MS patients with and without ''lifetime suicidal ideation'' could distinguish the groups by severity of depression, social isolation, and alcohol abuse. This study (based in the USA) also noted that patients with suicidal ideation often were not in receipt of psychiatric evaluation.

The differential diagnosis of depression in MS includes adjustment disorders, paroxysmal changes in mood (such as pathological crying or emotional lability), and mood changes in relation to drugs for MS.

A number of drugs used to treat MS or its symptoms have been implicated as risk factors for low mood. There are case

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**Table 3**  SSRI withdrawal symptoms

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| F | Flu-like symptoms |
| I | Insomnia |
| N | Nausea |
| I | Imbalance |
| S | Sensory disturbance |
| H | Hyperarousal |

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**Table 4**  Important clues to depression in multiple sclerosis

- ► Pervasive mood change
- ► Diurnal variation in mood
- ► Beck's ''cognitive triad''
- ► Mood congruent psychotic symptoms
- ► Suicidal ideation
- ► A change in function not related to physical disability

reports of steroid induced low mood in MS and other disorders. All the anti-spasticity drugs have been associated with low mood (including baclofen, dantrolene, and tizanidine). There are also case reports of psychiatric changes (including depression) following the abrupt discontinuation of baclofen and other anti-spasticity drugs. This means that history taking in respect to depression should include a detailed drug history.

There has been controversy over whether interferon treatment is a risk factor for depression in MS. Theoretically, interferon could lead to low mood via its effects on the kynurenine pathway (leading to depletion of available serotonin). Suicides, which occurred in the initial trials, appeared to bear this out. The most recent prospective studies indicate no relation between either interferon beta-1a or 1b and depression. Indeed one study, which used serial psychiatric assessments, indicated that the prevalence of depression decreased significantly over the course of the treatment with interferon beta-1b, although this may have represented a ''Hawthorne effect''.

### Risk factors for depression in MS

There appears to be a complex relation between disability, pain, fatigue, perception about prognosis, location of lesion, and depression in MS. Most of the magnetic resonance imaging (MRI) studies have not located a ''depressogenic'' MS lesion except for a possible relation between severity of depression and right temporal lesions.

### Treating depression in MS

There is only one double blind RCT of treatment of depression in MS. This trial compared desipramine plus psychotherapy to placebo plus psychotherapy.[5] Half the patients in the drug treatment arm did not reach the specified dose because of adverse effects. However there was a significant, if modest, effect in favour of desipramine.

There have been open label trials of a number of drug treatments including SSRIs (sertraline and fluoxetine). In general, SSRIs are easier to tolerate and are likely to be equally effective compared to tricyclic drugs.

Clinical experience would suggest that the best strategy would be to ''start low, go slow'' when initiating antidepressant treatment (unless the clinical severity of depression dictates otherwise). If side effects are encountered, judicious reduction in dose (rather than discontinuation) may be the best strategy.

Mild to moderate forms of depression (in people without significant cognitive impairment) may be managed with cognitive behavioural therapy (CBT). CBT can also work well in a group setting, enhancing its cost effectiveness. For more severe forms of depression and in those with cognitive impairment, drug treatments are probably the best first line treatment.

Other models of psychotherapeutic treatment have been used in people with MS (including individual psychotherapy, psychoanalysis, supportive psychotherapy, and education based groups). In general, experience has been favourable but there is very little evidence for or against effectiveness.

There are a few case reports of the use of ECT in the treatment of severe depression in people with MS. In many of the cases ECT was found to be effective in people who were otherwise clinically refractory. However, other MS symptoms worsened in around 20% of the reported cases.

## DEPRESSION AND STROKE

Stroke is characterised by sudden injury (often with consequent multiple loss of function) followed by a recovery phase. Injury tends to be focal. This leads to a different spectrum of neuropsychiatric problems when compared to inflammatory or neurodegenerative conditions.

There are three main reasons why people are at increased risk of depression following stroke:
- They often suffer sudden, multiple loss events (loss of physical function, employment, change in social or marital status)
- They may lose the neurological capacity to process these loss events
- Stroke may affect areas of the brain directly involved in control of mood.

### Epidemiology of depression post-stroke

Epidemiological studies of depression post-stroke are fraught with a variety of methodological problems related to ascertainment bias, rating of depression, and the heterogeneity of cerebrovascular disease. The peak incidence of depression is between six months and two years post-stroke and point prevalence for depression varies between 10–34% according to studies. In one large, US based, community epidemiological study, patients with depression post-stroke were more likely to be younger, more often white and less likely to be alive three years post-cerebrovascular accident (CVA) than those who were not depressed post-stroke.

Other risk factors for depression include functional and cognitive impairment, a past history of depression, and a lack of social support

### Does lesion location predict post-stroke depression?

There has been a lively debate on the subject of lesion location in relation to post-stroke depression. Data from the early 1980s first suggested that there was a relation between proximity of the lesion to the frontal pole and depression. This appeared to have been contradicted by a meta-analysis published in the *Lancet* in 2000.[6] This analysis was further criticised by others on the grounds that the hypothesis was not specific enough and that some relevant studies had been omitted. When a similar methodology was used but the data looked at separately for each hemisphere, there was a clear relation between proximity of the lesion to the left frontal pole and depression, especially in the first few months after stroke.[7] The results of this second meta-analysis were given further weight by a Finnish study published earlier this year.[8] This study also found that a brain infarct affecting the pallidum was a strong predictive factor for post-stroke depression (odds ratio 7.2). This finding also fits with case reports of dysphoria in relation to insertion of deep brain stimulating electrodes in the same area.

### Diagnosis of depression post-stroke

A number of factors can make the diagnosis of depression difficult post-CVA. Communication difficulties, impairments of facial and emotional expression, and disturbance in vegetative functions can make assessment of mental state extremely difficult. A deterioration in function over a few days or weeks following a period of improvement is one clinical clue for the development of depression.

Extreme abulia can sometimes be mistaken for depression and can be related to either frontal (especially left frontal) and diencephalic lesions. The patient may appear to be

extremely retarded but may function at a high level within a structured environment. Dopamine agonists, such as bromo-criptine, have been used to treat abulia.

Pathological emotionalism is relatively common after stroke, affecting up to 20% of patients in the first six months post-stroke but tending to improve over the following year. Severe examples of pathological emotionalism have been treated with antidepressant medication and levodopa.

**i52**

### Rating scales for depression post-stroke

Rating scales for depression have two main uses after stroke—as a screening instrument, and as a way of measuring change in symptoms over time. There are very few studies validating the use of rating scales for measuring change, but a number of studies have looked at validation of screening instruments.

On the whole there tends to be poor agreement between a variety of screening rating scales and clinical diagnosis based on operationalised criteria. For most of the scales that have been studied using receiver operating curves, sensitivity to depression is only gained by significant losses in specificity. A recent review of screening instruments produced for the Stroke Association (Bennett HE, Lincoln NB. Screening for mood disorders after stroke, personal communication, 2004) recommended the following screening measures:

► On acute hospital wards, the "signs of depression" scale could be administered weekly by nursing staff. Patients scoring 4 or more should be further assessed.

► In rehabilitation settings, the best validated scales were the hospital anxiety and depression scale (HADS) and the general health questionnaire-12 (GHQ-12). Patients with HADS score of 10 or over should be examined further. For those with communication problems, the visual analogue mood scale or hospital stroke aphasic depression questionnaire (SADQ) could be used. Patients scoring over 19 on the hospital SADQ should be assessed further.

► In the community, HADS and GHQ-12 are recommended. For those with communication problems, the stroke aphasic depression questionnaire-10 (SADQ-10) is recommended. Those scoring over six on the SADQ-10 should be referred for further evaluation.

### Preventing and treating depression after stroke

A recently published Cochrane review examined trials that looked at interventions to prevent depression after stroke.[9] They found 12 trials that fulfilled the criteria for inclusion (1245 participants). None of the included drug trials indicated a prophylactic effect of antidepressant medication, compared to placebo. However, one trial of psychotherapy (a kind of practical, problem solving therapy) had a small but significant effect size.

Since that review was published, a more recent study has compared the effect of early (first month) versus late (third month) antidepressant treatment on a functional outcome measure in 62 stroke patients.[10] They found that early, prophylactic treatment led to an enhanced functional outcome—an effect that persisted over the two years of the study.

Treatment trials have indicated that SSRI treatments (citalopram, sertraline) and other antidepressants (reboxetine) are superior to placebo. There have also been small trials supporting the use of transcranial magnetic stimulation.

## SUMMARY

Depressive syndromes in chronic neurological illness are common and disabling. Their aetiology is complex and may be multifactorial in individual patients. Good history taking (including history of presenting complaint, past psychiatric history, personal and social history, pre-morbid personality and treatment history), and detailed examination of physical and mental state (including cognitive function) will usually reveal the diagnosis and formulation.

Treatment and prevention of depression in neurological disorders is woefully under-researched relative to the morbidity it causes. However, providing the diagnosis of depression is correct, treatment can often be effective, leading to increases in function and quality of life.

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